Autoantibody synthesis accompanies many idiopathic chronic inflammatory diseases. Autoantibody assays are useful diagnostic tools. However, autoantibodies against intracellular components cannot cause the destruction of an intact cell under normal conditions. Epitope mapping of recombinant proteins has defined the principal antigenic determinants that are recognized by various autoantibodies. One aim of these studies has been to identify regions of autoantigens that might cross react antigenically with environmental pathogens. However, the results have been inconclusive, because most antibodies recognize complex three-dimensional structures that depend upon protein folding. It has proven very difficult to pinpoint a particular amino acid sequence that constitutes an entire autoantibody epitope.

T lymphocytes, as opposed to antibodies, recognize short linear peptides bound to class I or class II major histocompatibility complex (MHC) molecules. Interstitial tissue macrophages and dendritic cells, that ingest apoptotic cells, may have access to peptides derived from sequestered cytosolic antigens. A few hundred peptide molecules loaded on MHC antigens of dendritic cells can activate antigen-specific T helper cells. Cytokines released from activated T lymphoblasts may cause damage to adjacent normal cells, and can help B lymphocytes to proliferate and differentiate into plasma cells. Hence, recent epitope mapping studies of self-antigens have focused on autoreactive T lymphocytes, rather than autoantibodies.

In this issue of *The Journal,* Atkinson and co-workers report analyses of peripheral blood lymphocyte proliferative responses to 38 overlapping synthetic peptides from the 62-kD form of human glutamic acid decarboxylase (GAD). This cytosolic enzyme is a major autoantigen in insulin-dependent diabetes. Autoantibodies to GAD are an established risk factor for diabetes in first degree relatives of affected patients. The authors found that the peripheral blood lymphocytes from patients with early disease, and from their first degree relatives with anti-GAD antibodies, proliferated most frequently after incubation with a 16-residue synthetic peptide that contained the amino acid sequence PEVKEK (proline-glutamic acid-valine-lysine-glutamic acid-lysine) at the carboxyl end (1). The PEVKEK sequence is duplicated in the P2-C protein of Coxsackie B virus. One interpretation of the epitope mapping data is that exposure of genetically susceptible individuals to the viral antigen might trigger a T cell proliferative response to the autoantigen GAD. Transgenic mouse models lend support to this hypothesis (2).

However, the authors' data do not support a direct role for Coxsackie virus in the pathogenesis of insulin-dependent diabetes. Only a minority of diabetic patients or their relatives reacted with the peptide containing the PEVKEK sequence at the carboxyl end. Furthermore, very few individuals recognized an overlapping peptide with the PEVKEK epitope at the amino terminus. There was no serologic evidence to indicate that people at risk for insulin-dependent diabetes had a different level of exposure to Coxsackie virus than did control subjects. What, then, might be the role of Coxsackie virus, or other environmental agents containing T cell epitopes cross-reactive with self proteins, in the pathogenesis of autoimmunity?

Both the initiation of a specific immune response, and the expansion of memory T lymphocytes, require exposure to antigen. In some normal individuals, infection with Coxsackie B virus may expand the pool of memory T lymphocytes capable of recognizing the PEVKEK epitope. In people with normal pancreatic islet cells, the autoreactive T lymphocytes may be harmless. However, the augmented number of potentially autoreactive precursors might increase the chance of developing a self-sustaining immune response after GAD release from injured pancreatic islet cells, and the uptake of the antigen by dendritic cells. In patients with established but clinically insignificant islet cell inflammation, exposure to Coxsackie virus could boost immune responses to the PEVKEK region of the GAD molecule, thereby exacerbating disease.

Inbred mice of the non-obese diabetic (NOD) strain develop anti-GAD immune responses early in life, prior to the appearance of clinically significant diabetes. The induction of tolerance to GAD has been reported to reduce the incidence of diabetes in these animals (3). The mouse disease is genetic, and does not require exposure to Coxsackie virus, nor to any other unique environmental pathogen. However, one must be careful in extrapolating data from inbred mice to outbred human populations. Most likely, the common human autoimmune diseases represent the final outcome of several different genetic and environmental risk factors that alter disease susceptibility, severity, and outcome. Because T lymphocytes recognize short peptides, epitope mapping studies may identify the critical regions of self and non-self antigens that shape autoimmune responses. Even if environmental pathogens are not a direct cause of autoimmune disease, they still may represent targets for therapeutic intervention.

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